Explanation for Claim Amendments

Claims 77, 79, 113 have been amended to correct an inconsistency between the specification basis for the proportions and the manner of expression of the proportions in the claim. The previous claims defined the proportions in terms of the weight of drug to excipient, but in fact the numbers in the claims (and the specification) are the amount of drug in relation to the weight of the *entire* composition, i.e., the total of the active drugs, carriers and excipients. For example, specification formulation A contains 500 mg of TDF and emtricitabine and 500 mg of excipients and carriers, for a total weight of 1000 mg. Thus, the drugs are in a proportion of 500:1000 as currently stated in claim 77, et al., but this proportion is that of the drugs to *total* composition weight.

Claims 83, 96, 98 and 125 contained typographical errors which have been corrected by this amendment.

The feature of claim 62 (5 – 95% carrier material) has been introduced into independent claims 59, 73, 87, 98, 100, 109 and 123. It will be understood that carrier material is generic to carriers and excipients, and that these are the components of the composition other than the anti-viral compounds.

Sustiva is a trademark for the generic drug efavirenz. As a result, the claims are amended to use the generic term.

The remaining amendments are editorial.

None of these amendments introduces new matter, and are suitable for entry.

Withdrawn Rejections

Applicants gratefully acknowledge the withdrawal of rejections for double patenting and under 35 USC 103 over Chen et al.

Related Cases

Applicants brought USANs 11/453,122 and 11/452472 to the examiner's attention as containing related subject matter. The examiner's conclusions as to Applicants' reasons for doing so are the examiner's own speculations that may or may not reflect Applicants' thinking.

New Rejection Under 35 USC 103

The examiner has rejected Claims 59, 61-64, 66, 67, 70-88, 96 and 98-125 over Liotta et al. Becker et al. and Fiske et al. Liotta et al. was cited for its teaching of emtricitabine (FTC), its suggestion to make FTC tablets using various excipients, and to combine FTC with other (unspecified) antiviral compounds. Liotta et al. teaches that FTC is active against HIV, HBV and SIV. Becker et al. discloses that tenofovir disoproxil fumarate (TDF) is old. Fiske et al. discloses the use of Sustiva used to treat HIV.

Liotta et al. disclose by administering FTC solutions directly to animals (section VI). The disclosure on pages 50-51 relating to tablets and other dosage forms appears to be a standard disclosure. This standard disclosure section also contains a suggestion to mix FTC with "other materials that do not impair the desired action" ("action" meaning the antiviral effect of FTC), such as "other antivirals, including other nucleoside anti-HIV compounds" (page 52, third full paragraph).

As the examiner recognizes, Liotta et al. do not disclose the manufacture of an FTC tablet containing TDF, with or without Sustiva. Liotta et al. do suggest including "nucleoside" compounds. Nucleoside compounds typically contain a sugar analogue with a 5' hydroxymethyl group, analogous to naturally-occuring nucleoside structures.

It is currently believed that TDF would not be properly considered a nucleoside because it does not contain the 5' hydroxymethyl terminus. Instead, it terminates in a phosphonomethoxy group (and contains a linear aglycon rather than the sugar-like oxathiolane found in FTC). Thus, it is unclear that Liotta et al. contemplated co-formulation with TDF-like compounds at all. Liotta et al's disclosure of "antiviral" compounds is too general to have any instructive meaning.

Most importantly, Liotta et al. teach that anything to be included in the FTC dosage forms should not be expected to impair the FTC activity. While it is conceptually easy to contemplate mixing various drugs together into dosage forms, practical considerations prevail when it actually comes to formulating the compositions. While some formulations can be expected to be less likely to cause adverse interactions among drugs in the same composition, e.g., capsules containing mixtures of separately powdered drug compositions packaged under mild conditions, others require harsher manufacturing conditions and therefore present greater risks of adverse interactions among the drug substances.

Tableting involves exposure of the drug compounds to heat and pressure incidental to tablet compression. Some drug compounds may be reasonably expected to interact with one another under such conditions and later storage, becoming chemically unstable and leading to loss of potency and exposure of patients to degradation products. In such cases, those skilled in the art would tend to select different formulation methods, or take special steps during formulation to head off problems. Unexpected problems in fact may crop up that require intervention or special formulation steps after initial testing. Liotta et al. clearly contemplated that some additives might impair the desired antiviral effect of FTC. TDF would have been one of them, particularly under tableting conditions.

The chemical stability of TDF (tenofovir disoproxil fumarate) and FTC (emtricitabine) when tableted together would have been of concern due to their low pKa values of 3.75 and 2.65. To further elaborate on this matter, one should bear in

mind that TDF not only is a labile bis-ester, it also is the salt with fumaric acid, an organic diacid. Only one carboxyl group of the fumaric acid is consumed for salt formation. The remaining carboxyl group would have been expected (when in a combination product) to be free to catalyze (during manufacturing and storage) the deamination of FTC. The acid-catalyzed deamination of FTC forms FTU and ammonia. Ammonia in turn would have been expected to catalyze the hydrolytic degradation of TDF to mono-POC PMPA (the mono-ester of TDF), formaldehyde, isopropanol and carbon dioxide (carbonic acid). The carbonic acid would have been expected to further degrade the FTC, thereby creating more ammonia. The formaldehyde also would have been expected to cross-link FTC to produce dimers. The result of al this was that one could have expected a substantial prospect of reciprocal catalytic degradation involving reinforcing components from each of TDF and FTC.

A person skilled in the art, in possession of this knowledge, would have considered other alternatives to the combined formulation adopted by applicants. For example, the drugs could have simply been administered separately, see Ristig et al. (of record), or they might have been assembled separately into a patient package. It would not have been obvious to coformulate TDF and FTC in the same dosage form. On the contrary, it was surprising to find that, in spite of legitimate concerns about the combination of TDF and FTC is safe and stable (see page 45, lines 4 to 25).

A further problem was in fact encountered by applicants in the tableting of TDF and FTC – containing compositions. The TDF and FTC crystalline starting materials are alone relatively stable to degradation and long term storage. However, applicants found that optimal amounts of excipient substantially improve the storage stability of the combined tablets. Without being held to any particular theory of operation, applicants believe that the two crystalline drugs TDF and FTC form a eutectic mixture during manufacture into tablets. This eutectic mixture is believed to be amorphous, not crystalline, and therefore more labile to adverse storage conditions. Optimal results in this respect are believed to be obtained when the ratio of excipient to combined drugs is 50:50 (the embodiment of Table 2).

Applicants have amended independent claims 59, 73, 79, 87, 100, 109 and 123 to recite the presence of about 5% to about 95% carrier material. Alternatively, independent claims 98 and 125 describe the stabilizing effect of carrier material in a functional fashion (stability under defined harsh storage conditions). These claims are now believed to be patentable over the art of record. It would have been unobvious to combine FTC and TDF in the same tablet. Applicants request that this rejection be reconsidered and withdrawn.

This application is now believed to be in condition for allowance. An early Notice to that effect is solicited.

Respectfully submitted,

Max Hensley

Date: 8/17/07